REMARKS

Applicants have amended the specification. Amendments are made in response to objections to the drawings as explained in section II below and to more accurately conform the description to certain figures and examples, which amendments are indicated in the table below.

Paragraph	Phrase	Examples of Support in the Specification and References
Paragraph [065]	A loop (approximately 10μl) of fresh bacterial culture was individually inoculated. The bacterial culture was transferred	MPEP 2163.07 Paragraph [065] of original specification, rephrasing
Paragraph [071]	SDS-7.5% polyacrylamide gel The α form of the [[is]] [[a]] collagen monomer [[which]] weighs around 95 – 100 kDa. The β form ~~is a polymer which~~ weighs around 200 kDa. The extracted collagens are well-preserved α and β forms weighing respectively ~~collagen monomers~~ around 100 to 200 kDa.	Original Figure 2 Paragraph [071] was amended to more accurately conform the description to Figure 2 and the Example, particularly to the last two sentences of the paragraph.

Paragraph [076]	10% SDS-Page Lane 1 contains 20 µg of porcine collagen; lane 2 contains 40 µg of porcine collagen; lane 3 contains 40 µg of commercial bovine; and lane 4 contains 20 µg of commercial bovine. Collagen monomers, α form[[,]] and ~~polymers~~[[,]] β form, were extracted weighing around 100 and 250 kDa respectively (Fluka pure bovine collagen was used as a reference).	Original Figure 3 Original Figure 3 Paragraph [076] was amended to more accurately conform the description to Figure 3 and the Example.
Paragraph [080]	8% SDS-Page see Figure 4 Lanes 1 and 2 contain 10 µl and 20 µl of collagen respectively.	Original Figure 4 Original Figure 4
Paragraph [084]	8% SDS-Page Lane 1 contains 5 µl of collagen; lane 2 contains 10 µl of collagen; lane 3 contains 20 µl of collagen; and lane 4 contains 40 µl of collagen.	Original Figure 5 Original Figure 5
Paragraph [087]	8% SDS-Page Lane 1 is the marker; lane 2 contains 5 µl of collagen; and lane 3 contains 10 µl of collagen.	Original Figure 6 Original Figure 6

No new matter is added by the foregoing amendments.

In the Office Action mailed March 21, 2005, the Examiner rejected claims 1-40. In the present amendment, Applicants have canceled claims 1-53 without prejudice or disclaimer and added new claims 54-74. These claims are supported by the original claims and specification as indicated, for example, in the table below.

Claim	Phrase	Examples of Support in the Specification/Original Claims
54	A method of producing collagen monomers comprising: (a) providing microorganisms;	Original claim 1
54	(b) providing collagen-containing tissues obtained from animals selected from mammals, aquatic animals and avian animals;	Original claim 28
54	(c) allowing the microorganisms to ferment the collagen-containing tissues for a time sufficient to permit the production of a collagen composition weighing at least about 10% of the weight of the collagen-containing tissues,	Original claims 42, 43, 44
54	wherein the collagen composition comprises mostly collagen monomers which in an SDS-PAGE comprises predominantly α forms with a molecular weight of about 100 kDa;	Figures 2-6
54	(d) solubilizing the fermented tissues by the addition of an acidic solution and an enzyme preparation at low temperatures;	Original claim 16 Paragraphs [006], [034], [067]
54	(e) precipitating the mostly collagen monomers; and	Original claim 18
54	(f) obtaining the precipitated mostly collagen monomers.	Paragraph [009]
56	precipitation is carried out by the addition of salt	Original claim 18

57	the microorganisms are grown for more than 24, 48 or 72 hours before fermenting the collagen-containing tissues.	Paragraphs [065], [074], [077], [081], [085], [086]
58	fermentation is performed with agitation and aeration	Paragraphs [065], [066], [074], [075], [077], [078], [086]
59	The collagen composition weighs at least about 50% or at least about 80% of the weight of the collagen-containing tissues	Original claims 43, 44
60	wherein the low temperatures is at about 4°C	Paragraph [067]
61	the microorganisms comprise GRAS microorganisms	Original claim 6
62	the microorganisms comprise bacteria or yeast	Original claims 2, 5
63	the bacteria are Gram positive	Original claim 3
64	the bacteria are of the genus *Bacillus*	Original claim 4
65	the mammals are porcine	Original claim 9
66	the aquatic animals are fish or shark	Original claims 11, 12
67	the avian animals are chickens	Original claim 34
68	A method of producing collagen monomers comprising: (a) providing Gram (+) bacteria belonging to the genus *Bacillus* in a fermenter; (b) providing collagen-containing tissues from one or more of mammalian, aquatic, or avian animal sources; (c) allowing the bacteria to ferment the collagen-containing tissues at about 10% w/v to about 40% w/v in the fermenter for a time sufficient to permit	Original claim 35

68	the production of a collagen composition weighing about 20% to about 40% of the weight of the collagen-containing tissues,	Paragraphs [009] "...collagen yield is about 5 to 10 times of that ... by methods in the prior art." *See below:* Paragraphs [072] "...method described in US Pat. No. 5,106,949 ... is at greater than about 4%..." "U.S. Pat No. 5,436,135 describes ... 180g of final product ... extracted from 35.7 kg of placenta tissue..." Paragraphs [072] "...recovered ... collagen was 30% of the total initial tissues used."
68	wherein the collagen composition comprises mostly collagen monomers which in an SDS-PAGE comprises predominantly α forms with a molecular weight of about 100 kDa;	Figures 2-6
68	(d) solubilizing the fermented tissues at about 1% w/v to about 50% w/v in an acidic solution of about 0.5M acetic acid (pH 3.0)	Original claims 30
68	with pepsin provided at about 0.2% w/v to about 5% w/v at low temperatures;	Original claim 31 Paragraph [067]
68	(e) adding salt to the acidic solution sufficient to precipitate collagen and keeping it undisturbed overnight; and	Original claim 28
68	(f) obtaining the precipitated mostly collagen monomers.	Paragraph [009]
69	collagen-containing tissues are fermented at about 10% w/v in the fermenter for about 24 hours	Original claim 33

70	the acidic solution is about 3% w/v of about 0.5M acetic acid (pH3.0) with pepsin provided at about 1% w/v and further comprising stirring for about 48 hours when solubilizing the fermented tissues in the acidic solution	Original claim 33
71	the avian source is chicken	Original claim 34
72	the collagen-containing tissues are fermented at about 10% w/v to about 40% w/v in the fermenter for about 18 hours to about 48 hours	Original claim 39
73	the acidic solution is about 3% w/v of about 0.5M acetic acid (pH3.0) with pepsin provided at about 0.4% w/v to about 2% w/v and further comprising stirring for not more than about 48 hours when solubilizing the fermented tissues in the acidic solution	Original claim 39
74	the mammalian source is porcine	Original claim 40
75	wherein (a) and (b) are conducted simultaneously or sequentially, in either order	
76	wherein the low temperatures is at about 4°C	Paragraph [067]

With these amendments, claims 54-74 are pending.

I. Preliminary Matters

The Examiner made the restriction requirement final and acknowledged receipt and consideration of the references cited and the IDS submitted in July 16, 2004 and December 12, 2004.

II. Drawings

The Examiner stated that the drawings are objected to because they contain figure legends and/or explanations of the figures. The Examiner further stated that only the drawings and figure number should be present. Applicants submit herewith the replacement sheets with the corrected drawings, in compliance with the Examiner's request. In addition, Applicants have amended the specification to insert the information deleted from the drawings.

III. Claim Objections

The Examiner objected to claims 29 and 35-40 because of the informalities in the use of "160 μl"; claims 32-34 because of the informalities in the recitation of "X grams" of salt; and claims 28-34 because of the informalities resulting from the incorrect spelling of the word "*Bacillus*". Without acquiescing to the rejections, the rejected claims have been canceled and the phrases do not appear in any of the pending claims.

IV. Rejection of Claims 1-17 Under 35 U.S.C. § 102

The Examiner rejected claims 1-17 under 35 U.S.C. § 102(b) as allegedly being anticipated by a published UK patent application by John Cecil Bickley (Bickley), asserting that "Bickley teaches a process for the production of soluble collagen from a mammalian source by fermenting the collagen containing material in a fermentor with lactobacillus..." Office Action at page 5. Applicants respectfully traverse.

As set forth above, without acquiescing to the rejection and without prejudice for the later submission of the cancelled claims, Applicants have cancelled claims 1-17. New independent claim 54 now recites:

A method of producing collagen monomers comprising:

(a) providing microorganisms;

(b) providing collagen-containing tissues obtained from animals selected from mammals, aquatic animals and avian animals;

(c) allowing the microorganisms to ferment the collagen-containing tissues for a time sufficient to permit the production of a collagen composition weighing at least about 10% of the weight of the collagen-containing tissues, wherein the collagen composition comprises mostly collagen monomers which in an SDS-PAGE comprises predominantly α forms with a molecular weight of about 100 kDa;

(d) solubilizing the fermented tissues by the addition of an acidic solution and an enzyme preparation;

(e) precipitating the mostly collagen monomers; and

(f) obtaining the precipitated mostly collagen monomers.

As is well established, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See* MPEP § 2131 at 2100-73 (Rev. 2, May 2004); *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). As the Examiner acknowledges, Bickley does not set forth "separation methods which involve using acetic acid and pepsin to remove the non-collagen peptides followed by filtration and then precipitation of the collagen by salt precipitation, and subsequent re-filtration of the collected and precipitated collagen." Office Action at page 6. Accordingly, Bickley cannot teach each and every element of the new independent claim and, thus, cannot anticipate the presently pending claims. Applicants respectfully request withdrawal of this rejection under 35 U.S.C. 102(b).

V. Rejection of Claims 1-40 Under 35 U.S.C. § 103

The Examiner rejected claims 1-40 under 103(a) as being unpatentable over Bickley in view of Ries and further in view of Petersen et al. Office Action at page 5. The Examiner alleges that it would have been obvious to use the method of Bickley and substitute it with the micro-organism from the genus *Bacillus* because "Petersen et al. clearly show that the proteinases produced from this genus are suitable for fermentation of collagen." Office Action at page 7. The Examiner further alleges that the collagen obtained by the process of Bickley and Petersen et al. can be purified according to the teachings of Ries, which she characterized as "a conventional purification method." Office Action at page 7.

Applicants respectfully traverse because the Examiner has not set forth a *prima facie* case of obviousness. Under 35 U.S.C. § 103, the Office bears the initial burden of establishing a *prima facie* case of obviousness. MPEP § 2142 at 2100-128-129 (Rev. 2, May 2004); *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). To make out a *prima facie* case, the PTO must satisfactorily show that:

> (1) the cited reference or combination of references teaches or suggests every limitation of the claim;
>
> (2) the references relied upon, coupled with the knowledge generally available in the art at the time of the invention, contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references; and
>
> (3) the proposed modification of the references has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made.

MPEP § 2143 at 2100-129; *Karsten Mfg. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001); *Amgen Inc. v. Chugai*, 927 F.2d 1200, 1209 (Fed. Cir. 1991); *In re* Wilson, 424 F.2d 1382, 1385 (C.C.P.A. 1970).

Here, the Examiner has not established the prima facie case of obviousness because she has not shown, *inter alia*, any motivation or reasonable expectation of success in this combination of references.

First, the Examiner relies on Petersen for allegedly showing that "proteinases from this genus are suitable for fermentation of collagen." Applicants respectfully note, however, that Petersen does not use proteinases to "ferment" collagen and does not produce collagen monomers. Instead, Petersen describes "conditioning of collagen for gelatin extraction," *see* col. 1, lines 3-4, and that strict focus on "conditioning" for the extraction of "gelatin" is maintained throughout. *See* Col. 1, lines 16-17, 36-37, 40-41, 48-51, 52-54, 55-56, and 6061. The specification further explains how enzymatic conditioning is an alternative to "alkaline treatment **conversion** of collagen sources to gelatin." Col. 1, lines 19-21. This is entirely consistent with a common definition of gelatin as "a mixture of proteins obtained by **hydrolysis of collagen** by boiling." Hawleys' Condensed Chemical Dictionary (12th Ed. 1993) (attached). Hawley's definition of collagen similarly notes that collagen "is **converted** to gelatin by boiling water which causes hydrolytic cleavage of the protein to a mixture of degradation products." Thus, Petersen would not teach or suggest the use of enzymes to "ferment" collagen-containing materials to obtain "collagen monomers." Moreover, its sole focus on conditioning of collagen to extract gelatin can provide neither motivation nor any reasonable expectation of success.

Then, the Examiner states the "motivation to combine the teachings [from Bickley, Petersen et al., and Ries] comes from Ries' teachings that his process is an improvement over the prior art process and that the collagen can come from any collagen-containing tissues." Office Action at page 7.

Ries, cannot, however provide any motivation to combine for several reasons. First, the entire teaching of Ries focuses on the production of a collagen product that must satisfy "**all**" of a number of specific properties. It states:

> In order to obtain optimum results in wound healing by means of collagen, a collagen product would have to be available which should meet **all** the requirements specified hereinafter:
>
> 1. it should have a high haemostatic activity;
>
> 2. it should have a high absorption capacity for body fluids;
>
> 3. it should promote the regeneration of tissues, especially of bone tissues;
>
> 4. it should have a high resorbability;
>
> 5. it should have as low an antigenic activity as possible; and
>
> 6. it should have optimum mechanical properties so as to make it suitable for the application to or the introduction into wounds or into bone cavities.
>
> The prior art collagen products either described in the literature or available on the market, while meeting one or a restricted number of the requirements set forth above, do not meet **all** of them at the same time.

See col. 1, lines 24-43. Ries thereafter provides that the collagen product made by its precisely described method meets these requirements at col. 3, liens 28-44. Thus, a skilled person would consider Ries only if they were similarly seeking a collagen product with all of these characteristics.

Second, Ries does not provide any motivation to combine with Peterson. As noted above, the Peterson enzymes function to condition collagen for the extraction of

gelatin, i.e., the enzymes convert the collagen sources to gelatin. In contrast, the Ries disclosure expressly uses enzymes to "do not attack the basic structure of collagen in order." Col. 1, lines 63-66. Ries notes later that the proteolytic enzymes avoids the "filamentous collagen molecules being split into smaller peptide fragments." Col. 2, lines 44-50.

Finally, the Examiner has not indicated that the combination would provide any reasonable expectation of success.

For at least the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness with respect to the new independent claim and, thus, the presently pending claims also can not be obvious. Applicants respectfully request withdrawal of this rejection under 35 U.S.C. 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims 54-76. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner contacts her or her supervising attorney Jean Fordis at (650) 849-6607 to set up an interview.

Please grant any extensions of time required to enter this response and charge

any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 21, 2005

By: _____
Anna Tsang
Reg. No. 48,003